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REGULATION OF IMMUNE RESPONSES TO PROTOZOAL PATHOGENS SEMINAR

FINAL REPORT

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Summary of speaker presentations

Dr. Richard Titus

The role of parasite-specific T cells in the immune response to *Leishmania major* was studied in the mouse model system. Parasite-specific CD4+ T cell clones were derived from genetically-resistant C3H mice infected with *L. major*. Protective T cell clones were found to secrete interleukin-2 (IL-2), interferon-γ (IFN-γ), tumor necrosis factor (TNF) and migration inhibition factor (MIF). Exacerbative T cell clones secreted IL-2 and IL-4 but not IFN-γ, TNF or MIF. Curiously, exacerbative CD4+ T cell clones derived from genetically-susceptible BALB/c mice were found to produce IL-2 and IFN-γ, but not IL-4. Finally, the role of mast cells in cutaneous leishmaniasis was also investigated. It was found that the course of disease was much less severe in mice that are genetically deficient in mast cells compared to congeneic mast cell-bearing control mice.

Dr. Rick Tarleton

The acute phase of T. cruzi infection is characterized by a profound but selective suppression of immune responses. The most prominent feature of this suppression is the regulation of IL-2 production. The regulation of IL-2 production may be indicative of an overall regulation of the TH1 compartment but is not a result of a strong TH2 response and is a result of either transcriptional or post-transcriptional (mRNA stability) regulation. T cells other than the TH1 and TH2 populations appear to contribute strongly to the immune response in T. cruzi-infected mice, before, during, and after the period of intense immunosuppression.

The cellular immune response to*Toxoplasma gondii* . LLOYD H. KASPER* and IMTIAZ A. KHAN. Dartmouth Medical School, Hanover, NH 03756
The importance of the cell mediated immune response to *T. gondii* is well recognized. Over the past several years, we have identified a variety of parasite antigens that are critical in eliciting this response, in particular P30. This tachyzoite membrane antigen has an approximate Mr of 30Kd, comprises 3-5% of the total parasite protein and is excreted into the parasitophorous vacuole. It is the major seroreactive protein identified by infected humans and experimental hosts. In humans and mice, this protein induces the production of high titer IFN-gamma as well as parasiticidal cytotoxic T cells. CD8+ cytotoxic T cells derived from immunized mice kill infected syngenic APC in an MHC restricted fashion. P30 used with the appropriate adjuvent is able to induce near 100% protection against acute and chronic toxoplasmosis in mice. This protective response is mediated by antigen-specific cytotoxic CD8+ T cells that can be adoptively transfered into naive recepients. These CD8+ T cells produce high titer IFN-gamma and are cytotoxic and kill extracellular *T. gondii.*

Dr. Fidel Zavala

ABSTRACT

Immunization of BALB/c mice with radiation-attenuated Plasmodium yoelii sporozoites induces cytotoxic T. lymphocytes (CTL) specific for an epitope located within the amino acid sequence 277-288 of the P. yoelii circumsporozoite (CS) protein. Several $CD8^+$ CTL clones were derived from the spleen cells of sporozoite-immunized mice, all displaying an apparently identical epitope specificity. All the clones induced high levels of cytolysis "in vitro" upon exposure to peptide incubated MHC compatible target cells. The adoptive transfer of two of these clones conferred complete protection against sporozoite challenge to naive mice. This protection is species and stage specific. Using P. yoelii specific ribosomal RNA probes to monitor the "in vivo" effects of the CTL clones, we found that their target was the intrahepatocytic stage of the parasite.

Onesmo OleMoi-Yoi ILRAD, Nairobi, Kenya

Immunity to intracellular protozoal pathogens: Theileria parva

Theileria parva, the causative agent of East Coast Fever (EVF) in cattle, is an intracellular protozoan parasite which induces lymphoblastogenesis and clonal expansion of infected cells. Such cells are immortalized and, therefore, can be propagated indefinitely in vitro. T. parva-infected cells are pleiomorphic, have short (16-25 hr) generation times, form tumor-like masses which metastasize and infiltrate organs upon injection into athymic mice and exhibit alterations in surface phenotype. These cells are thus considered to be transformed.

In our attempts to determine the mechanism of T. parva-induced transformation, we have identified a parasite casein kinase (CK) II enzyme which, along with its bovine homolog, is highly active in infected cells. It has recently been shown that among the substrates of CKII are nuclear proteins most of which may be involved in the regulation of gene expression and cell growth.

Interestingly, several of these proteins from oncogenic viruses appear critical to the transformation process itself as well as to the capacity of such cells to elicit cytotoxic host cell responses. Because immunity to T. parva, like that of several other intracellular protozoal parasites, appears to have a substantial cellular componenet, we have identified and are in the process of characterizing CKII substates as potential candidates mediating recognition, in conjunction with MHC class I molecules, by cytotoxic T lymphocytes.